Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies

RESEARCH

Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies

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Abstract

Objective To examine and quantify the potential dose-response relation between fruit and vegetable consumption and risk of all cause, cardiovascular, and cancer mortality.

Data sources Medline, Embase, and the Cochrane library searched up to 30 August 2013 without language restrictions. Reference lists of retrieved articles.

Study selection Prospective cohort studies that reported risk estimates for all cause, cardiovascular, and cancer mortality by levels of fruit and vegetable consumption.

Data synthesis Random effects models were used to calculate pooled hazard ratios and 95% confidence intervals and to incorporate variation between studies. The linear and non-linear dose-response relations were evaluated with data from categories of fruit and vegetable consumption in each study.

Results Sixteen prospective cohort studies were eligible in this meta-analysis. During follow-up periods ranging from 4.6 to 26 years there were 56 423 deaths (11 512 from cardiovascular disease and 16 817 from cancer) among 833 234 participants. Higher consumption of fruit and vegetables was significantly associated with a lower risk of all cause mortality. Pooled hazard ratios of all cause mortality were 0.95 (95% confidence interval 0.92 to 0.98) for an increment of one serving a day of fruit and vegetables (P=0.001), 0.94 (0.90 to 0.98) for fruit (P=0.002), and 0.95 (0.92 to 0.99) for vegetables (P=0.006). There was a threshold around five servings of fruit and vegetables a day, after which the risk of all cause mortality did not reduce further. A significant inverse association was observed for cardiovascular mortality (hazard ratio for each additional serving a day of fruit and vegetables 0.96, 95% confidence interval 0.92 to 0.99), while higher consumption of fruit and vegetables was not appreciably associated with risk of cancer mortality.

Conclusions This meta-analysis provides further evidence that a higher consumption of fruit and vegetables is associated with a lower risk of all cause mortality, particularly cardiovascular mortality.

Introduction

Increased consumption of fruit and vegetables has been recommended as a key component of a healthy diet for the prevention of chronic diseases.[1 2] Cardiovascular disease and cancer are the two leading causes of death worldwide.[3] Factors that can reduce the occurrence of these important diseases could contribute to important improvements in health and longevity.

In recent years, there has been growing evidence that fruit and vegetable consumption is related to mortality, including mortality from cardiovascular disease and cancer.[4-6] The results, however, are not entirely consistent. While several studies found

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Appendix 1: Supplementary tables A-C
Appendix 2: Supplementary figures A-J

that consumption was associated with a lower risk of mortality,[7-9] no significant differences in risk of mortality were observed between vegetarians and non-vegetarians in a British population.[10] In most studies, the association has been examined by categorising the main variable into fourths or fifths of daily consumption.[11-13] There exists much uncertainty about the dose-response relation between consumption and the risk of mortality, especially for cancer, as recent large prospective studies have found no or minimal effects of consumption on overall cancer incidence or mortality.[14-16]

Understanding the relation between fruit and vegetable consumption and mortality is important for guiding consumer choices and prioritising dietary guidelines to reduce risk. We performed a meta-analysis of prospective cohort studies to quantify the dose-response relation between fruit and vegetable consumption and risk of all cause, cardiovascular, and cancer mortality.

Methods

Search strategy

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[17] for performing and reporting the present meta-analysis. We carried out a meta-analysis of prospective cohort studies that examined the associations of fruit and vegetable consumption with risk of all cause, cardiovascular, and cancer mortality. We systematically searched databases, including Medline (from 1950), Embase (from 1980), and the Cochrane Library (from 1960), between May 2013 and 30 August 2013 (last date searched). We used a search strategy that included truncated free text and exploded MeSH terms relevant to "fruits", "vegetables", "cardiovascular disease," "coronary disease," "myocardial ischemia," "stroke," "neoplasms," "cause of death," "mortality," "humans," "epidemiology," "follow-up studies," "prospective studies," and their variants. No restrictions were imposed on language of publications. We indentified additional articles by manually searching the reference lists from recent reviews and the extracted papers.

Study selection

We excluded letters, comments, reviews, meta-analyses, ecological studies, and animal studies. Studies were included if they were cohort studies, studied the effects of levels of fruit and vegetable consumption, and reported mortality from all causes, cardiovascular disease, or cancer as the outcomes of interest . To identify eligible studies, we used a two step selection process. Two independent investigators (GZ, JL) conducted an initial screening of all titles or abstracts and then evaluated all potentially relevant articles based on full text reviews. Studies were excluded if they did not meet all criteria.

Data extraction and quality assessment

Data extraction was conducted with a standardised data collection form. Two authors (GZ, JL) independently performed the extraction of data. We used hazard ratios as a measure of the association. The primary exposure variable was total fruit and vegetable consumption, but we also examined total fruit and total vegetables separately. Outcomes of interest in this study were all cause, cardiovascular, and cancer mortality. All outcomes were classified based on the World Health Organization's international classification of disease criteria.

We recorded the following characteristics in the identified studies: first author, cohort name, country, publication year, age at entry, sex, sample size of the cohort, outcomes, duration of follow-up, method of assessment of fruit and vegetable consumption, ascertainment of outcomes, and variables that entered into the multivariable model as potential confounders. Regarding inclusion of studies and interpretation of data, a third investigator (YYO) was consulted to resolve discrepancies. Any disagreements were settled through consensus with all three authors. We assessed study quality with the Newcastle-Ottawa quality assessment scale.[18] The system allowed a total score of up to 9 points (9 representing the highest quality). We derived a score that summarised eight aspects of each study.

Statistical methods

We used STATA version 12.0 (StataCorp LP, College Station, TX) to analyse the data. In this meta-analysis, we used hazard ratios and 95% confidence intervals as a measure of the effect size for all studies. The study by Strandhagen and colleagues did not report the relative risks or hazard ratios and confidence intervals in each consumption category,[9] so we calculated the relative risks by using the total number of patients and the numbers of events.[19] Another study by Colditz and colleagues reported only hazard ratios but not corresponding 95% confidence intervals.[20] We calculated 95% confidence intervals by using P values and effect estimates.[21] All other studies included in the meta-analysis reported hazard ratios, estimated from Cox proportional hazards models, and corresponding 95% confidence intervals. We used the results of the original studies from multivariable models with the most complete adjustment for potential confounders. We used the inverse variance weighted method to obtain overall hazard ratios and 95% confidence intervals for an increase in consumption of one serving a day of fruit and vegetable. A random effects model accounted for variation between studies as this can provide more conservative results than a fixed effects model.[22]

The dose-response relation was estimated by using generalised least squares trend estimation, according to the methods developed by Greenland and Longnecker.[23-25] We used the two stage generalised least squares trend estimation method, which first estimated study specific slope lines and then combined with studies in which the slopes were directly reported to obtain an overall average slope.[25] Data on the amount of fruit and vegetable consumption, distributions of cases and person years, and hazard ratios and 95% confidence intervals were extracted to apply this method. We assigned the median consumption in each category of fruit and/or vegetable consumption to the corresponding hazard ratio for each study. If medians for that category were not reported, we estimated approximate medians by using the midpoint of the lower and upper bounds. If the highest category of the studies was open ended, we considered the difference from the lowest range to the median to be equivalent to the same difference in the closest adjacent category. If fruit and vegetable consumption was reported by servings or times, we converted it into the standard serving for the dose-response analysis, which was defined as 77 g for vegetables and 80 g for fruit.[26]

In addition, we examined non-linear associations between fruit and vegetable consumption and all cause mortality using a two stage random effects dose response meta-analysis. This was done by modelling consumption with the use of restricted cubic splines with three knots at fixed centiles (10%, 50%, and 90%) of the distribution.[27 28] We first estimated a restricted cubic spline model with a generalised least squares regression, considering the correlation within each set of published hazard ratios.[25] We then combined the study specific estimates, using the restricted maximum likelihood method in a multivariate random effects meta-analysis.[22] We estimated the pooled hazard ratios for servings of fruit and vegetables a day using a procedure to tabulate and plot results.[29] A test for a non-linear relation was calculated by making the coefficient of the second spline equal to zero.

We evaluated heterogeneity between studies with Cochran's Q test (P<0.10)[30] and used I^2 to quantify the proportion of the total variation due to that heterogeneity.[31] To explore the sources of heterogeneity among studies and test the robustness of the associations, we conducted subgroup analyses and several sensitivity analyses. We also examined the influence of individual studies on the overall risk estimate, which was investigated by recalculating the pooled estimates for the remainder of the studies by omitting one study at each turn.

Potential publication bias was assessed by the application of contour-enhanced funnel plots,[32] Egger's linear regression test,[33] and Begg's rank correlation test at the P <0.10 level of significance.[34] If publication bias was indicated, we further evaluated the number of missing studies in a meta-analysis by the application of the trim and fill method and recalculated the pooled risks estimate with the addition of those missing studies.[35] Except where otherwise specified, a P value <0.05 was considered significant.

Results

Literature search

Figure 1⇓ shows study selection process and results from the literature search. We identified 2019 articles from the Medline database, 3037 articles from the Embase database, and 2361 articles from the Cochrane Library. After exclusion of duplicates and papers that did not meet the inclusion criteria, we obtained 25 full articles of potentially relevant studies. After full text reviews, we excluded nine: one article with insufficient data for specific levels of fruit and vegetable consumption[36]; six articles that reported results of mixed diet,[37-39] specific cancer mortality,[40] or a marker of fruit and vegetable consumption[5] or enrolled patients with diabetes[41]; and two further articles[4 42] with data from the same cohort used in other studies. Sixteen articles with 56 423 deaths (11 512 from cardiovascular disease and 16 817 from cancer) reported from 833 234 participants were included for the meta-analysis.[7-9 11-13 20 43-51]

Characteristics of the included studies

Tables 1⇓ and 2⇓ show the characteristics of the included studies, all of which had a prospective cohort design. The total number of participants (from 501 to 451 151) and deaths (from 42 to 25 682) varied widely across cohorts. The duration of follow-up ranged from 4.6 years to 26 years. Four studies included only men, and 12 studies included men and women. Six studies were conducted in the United States,[7 8 20 45 46 51] four in Asian countries,[11-13 47] and six in Europe.[9 43 44 48-50] Three studies measured consumption of fruit and vegetables by diet records,[45 48 51] and all other studies used food frequency questionnaires.

All studies adjusted for age, except for one study of men born in 1913 because all the participants were at the same age.[9] Most cohorts controlled for some conventional risk factors, including body mass index (n=12), smoking (n=13), and alcohol consumption (n=12). Some cohorts also adjusted for physical activity (n=8) and energy intake (n=9), but few studies adjusted for other dietary variables or nutrients (n=6).[11-13 43 45 48]

Assessment of study quality yielded an average score of 7.1, and 10 studies had a score of 6.5 or above (see table A, appendix 1).

Fruit and vegetable consumption and risk of all cause mortality

Table 3⇓ shows the results of the pooled analysis for all the included studies. The relation between fruit and vegetable consumption and risk of all cause mortality was evaluated in seven studies,[7 8 43-46 48] comprising 553 698 participants and 42 219 deaths. The pooled hazard ratio of all cause mortality was 0.95 (95% confidence interval 0.92 to 0.98; P=0.001; fig 2⇓) for an increment of one serving of fruit and vegetables a day, with significant heterogeneity (P<0.001, I^2=82%).

Begg's rank correlation test indicated no publication bias (P=0.76), but Egger's linear regression test indicated possible publication bias for the association (P=0.006). We used the trim and fill method to recalculate our pooled risk estimate. The analysis suggested that the imputed risk estimate was 0.95 (95% confidence interval 0.92 to 0.98), which is identical to our original risk estimate. No missing studies were imputed in the contour enhanced funnel plot (see fig A, appendix 2).

Using a restricted cubic splines model, we observed some evidence of a curvilinear association between total consumption of fruit and vegetables and risk of all cause mortality (P=0.01 for non-linearity; fig 3⇓). There was a dose-response relation between consumption of fruit and vegetables and decreasing risk of all cause mortality at consumption below five servings a day, but the risk did not decrease further with five or more servings a day. Compared with people who had no daily consumption of fruit and vegetables, the estimated hazard ratios of all cause mortality were 0.92 (95% confidence interval 0.90 to 0.95) for one serving/day of fruit and vegetables, 0.85 (0.81 to 0.90) for two servings/day, 0.79 (0.73 to 0.86) for three servings/day, 0.76 (0.69 to 0.83) for four servings/day, 0.74 (0.66 to 0.82) for five servings/day, and 0.74 (0.65 to 0.82) for six or more servings/day.

Seven studies reported data for fruit or vegetable consumption and all cause mortality.[9 11 13 43 45 49 51] The summary estimates were 0.94 (95% confidence interval 0.90 to 0.98; P=0.002; fig 4⇓) for each additional serving a day of fruit and 0.95 (0.92 to 0.99; P=0.006; fig 5⇓) for vegetables. There was significant heterogeneity for both analyses (P<0.001, I^2=77% for fruit and P<0.001, I^2=86% for vegetables).

For fruit consumption, we found no significant evidence of publication bias using Begg's rank correlation test (P=0.54), but Egger's linear regression test indicated possible publication bias (P=0.02). The application of the trim and fill method did not change the risk estimate (pooled hazard ratio 0.94, 95% confidence interval 0.90 to 0.98). No missing studies were imputed in the contour enhanced funnel plots (see fig B, appendix 2). For vegetable consumption, no significant publication bias was detected (Begg test P=0.13; Egger test P=0.36).

We also found evidence of a non-linear association for fruit (P=0.01 for non-linearity; see fig C, appendix 2) or vegetable consumption (P=0.01 for non-linearity; see fig D, appendix 2) with risk of all cause mortality. A lower risk of all cause mortality was observed in association with higher fruit consumption at about two servings a day (hazard ratio 0.83, 0.78 to 0.88) and vegetable consumption at about three servings a day (0.75, 0.66 to 0.86).

Fruit and vegetable consumption and risk of cardiovascular mortality

Total consumption of fruit and vegetables was investigated in four studies[7 8 43 48] with a total of 469 551 participants and 6893 cardiovascular deaths. Fruit consumption was examined in six studies[9 11-13 43 51] with 677 674 participants and 9744 cardiovascular deaths, and vegetable consumption was examined in six studies[9 11-13 43 51] with of 677 674 participants and 9744 cardiovascular deaths.

The average reduction in the risk of cardiovascular disease mortality was 4% (hazard ratio 0.96, 95% confidence interval 0.92 to 0.99; P=0.02) for each additional serving per day of fruit and vegetables combined (see fig E, appendix 2), 5% (0.95, 0.91 to 1.00; P=0.03) for fruit consumption (see fig F, appendix 2), and 4% (0.96, 0.93 to 0.99; P=0.01) for vegetable consumption (see fig G, appendix 2).

Fruit and vegetable consumption and risk of cancer mortality

Two studies reported data on the association between cancer mortality and total consumption of fruit and vegetables,[8 43] seven studies on fruit,[9 13 43 47 49-51] and eight studies on vegetables.[9 13 20 43 47 49-51] The hazard ratio for cancer mortality was 0.97 (95% confidence interval 0.90 to 1.03; P=0.31; see fig H, appendix 2) for each additional serving/day of total consumption, 0.99 (0.97 to 1.00; P=0.06; see fig I, appendix 2) for fruit, and 0.99 (0.97 to 1.01; P=0.19; see fig J, appendix 2) for vegetables.

Subgroup and sensitivity analyses

Table 4⇓ shows the different subgroup analyses of studies on all cause mortality. The associations between fruit and vegetable consumption and risk of all cause mortality did not differ substantially by study location, sex, number of participants, duration of follow-up, or study quality.

To explore potential source of heterogeneity across studies, we carried out several sensitivity analyses (see table B, appendix 1). Heterogeneity between studies was mainly caused by one large study.[43] For all cause mortality, after we excluded this study from the analysis there was no longer any evidence of significant heterogeneity for the combined consumption of fruit and vegetables (I^2 82%-0%), or for fruit consumption (I^2 77%-0%). Exclusion of this study from the pooled estimate had little impact on the overall effect size.

To examine the impact of multivariable adjustment, we conducted additional sensitivity analyses by excluding studies that did not adjust for physical activity or energy intake. We also examined studies with some form of adjustment for socioeconomic status (such as education or income level). Overall, the sensitivity analyses did not lead to any change in the significance or direction of effect for the association between the combined consumption of fruit and vegetable and risk of all cause mortality (see table B, appendix 1).

To further confirm the robustness of the results, we conducted a series of sensitivity analyses by excluding one study that did not report hazard ratios.[9] Exclusion of this study did not appreciably alter the results for total, cardiovascular, or cancer mortality (see table C, appendix 1).

Discussion

This meta-analysis supports the theory that higher consumption of fruit and vegetables is associated with a reduced risk of mortality from all causes and cardiovascular disease. The risk of all cause mortality was decreased by 5% for each additional serving a day of fruit and vegetables, by 6% for fruit consumption, and by 5% for vegetable consumption. We observed a threshold at around five servings a day, after which there was no further reduction in risk. While we found a significant inverse association for cardiovascular mortality, higher consumption was not appreciably associated with risk of cancer mortality.

Exploration of heterogeneity and publication bias

In the meta-analysis of all cause mortality, one study with a large sample size contributed to most of the observed heterogeneity.[43] Our results showed that about 82% of the variance in heterogeneity was due to the variation between studies.[52] Sensitivity analyses showed that exclusion of this large study did not appreciably alter the pooled hazard ratios.

There were no missing studies imputed in regions of the contour enhanced funnel plots. Egger's linear regression test indicated that the P value was significant. No publication bias was found for Begg's rank correlation test. Also, the application of the trim and fill method did not change the average effect size, further suggesting that results were not affected by publication bias.

Results in relation to other studies

Adherence to a Mediterranean diet, with a relatively large amount of fruit and vegetables, has been shown to significantly decrease the risk of total mortality and mortality from cardiovascular diseases.[53] In older people from several European countries, lower mortality was related with greater adherence to a Mediterranean diet.[38] Overall, about 10-30% lower risk of all cause mortality was found in most prospective studies comparing highest with lowest fruit and vegetable consumption.[4 7-9 11 49] A small study (n=713) that used total serum concentrations of carotenoids as biomarkers of fruit and vegetable consumption further supported a risk reduction in mortality, with a hazard ratio of 0.50 for women in the highest third of serum concentration compared with the lowest third.[5] The findings from our meta-analysis were consistent with a recent study showing that a lower consumption compared with five servings of fruit and vegetables a day was associated with higher mortality in a dose-response manner.[44]

For the reduction in total mortality, we found a threshold of around five servings a day of fruit and vegetables, after which the risk of death did not reduce further. Possible mechanisms might involve the availability of nutrients and the digestibility of fruit and vegetables,[54 55] but further studies are needed to confirm our results.

Our study also showed that higher consumption of fruit and vegetables was associated with lower risk of mortality from cardiovascular disease but not cancer. The risk of cardiovascular mortality was decreased by 4% for each serving a day of the combined consumption of fruit and vegetables, by 5% for fruit, and by 4% for vegetables. In a previous meta-analysis of eight cohort studies, individuals who consumed more than five servings a day had a 26% lower risk of stroke than those who consumed less than three servings a day.[26] In another meta-analysis of nine cohort studies on coronary heart disease,[56] a 4% lower risk was reported for each additional serving a day of fruit and vegetables, with a standard serving calculated as 106 g. As for the mechanisms for the inverse association between consumption of fruit and vegetables and cardiovascular mortality, antioxidant compounds and polyphenols in fruit and vegetables—such as vitamin C, carotenoids, and flavonoids—have been shown to prevent the oxidation of cholesterol and other lipids in the arteries[57] and to increase the formation of endothelial prostacyclin that inhibits platelet aggregation and reduces vascular tone.[58] Results from large randomised controlled trials have shown that increased consumption of fruit and vegetables can contribute to a small decrease in blood pressure.[59 60] Fruit and vegetables are good sources of magnesium and potassium, which have been inversely associated with mortality in previous studies.[61-63] Plasma concentrations of antioxidants, such as alpha carotene and beta carotene, increase in parallel with increased consumption of fruit and vegetables,[60 64] and this could reduce the risk of cancer and cardiovascular disease. Some other components in fruit and vegetables such as vitamin C, carotenoids, and other phytochemicals also probably contribute to a reduced risk of mortality.[4]

The association between higher consumption of fruit and vegetables and risk of cancer has not been firmly established. Results from epidemiological studies are inconsistent, particularly for hormone dependent cancers such as breast and prostate cancer.[65] Several studies showed no significant association between the consumption of either fruit or vegetables and total cancer risk,[16 66] whereas the Greek EPIC cohort study[67] reported a significant reduction in total cancer risk associated with high consumption of both fruit and vegetables. In the EPIC study from 10 European countries,[15] there was a weak inverse association between high consumption and total cancer risk. In our study, the pooled results indicate that higher consumption of fruit and vegetables was not appreciably associated with risk of cancer mortality, which suggests that increasing the amount of fruit and vegetables alone in an individual's diet might not provide an appreciable benefit on reducing cancer mortality.[65] In addition to the recommendation of consuming adequate amounts of fruit and vegetables, the adverse effects of obesity, physical inactivity, smoking, and high alcohol intakes on cancer mortality should be further emphasised. It is possible, however, that fruit and vegetable consumption might have stronger effects on specific cancer sites. In addition, different types of fruit and vegetables might have different effects on cancer risk. Future studies are needed to be more specific about types of cancer and the role of different groups of fruit and vegetables.

Strengths and limitations of the review

This meta-analysis was based on several prospective cohort studies from various populations. The combined sample size was large and the follow-up period was long enough. The estimates from the fully adjusted models for each study were used in our analyses to reduce the potential of confounding. The dose-response analysis was conducted to evaluate the linear and non-linear relations. This can help to quantify the associations and test the shape of these possible associations. To examine the potential sources of heterogeneity and evaluate robustness in the subgroups, we performed several sensitivity analyses.

There were, however, several limitations of this meta-analysis. Because in most studies fruit and vegetable consumption was assessed by food frequency questionnaires, errors in measurement were inevitable. The imprecise measurement of consumption might have attenuated the true associations. In addition, few studies adjusted for other dietary factors, such as saturated fat intake and consumption of processed meat, etc. The inverse association between fruit and vegetable consumption and mortality could be related to a generally more healthy diet and lifestyle. Because all included studies were observational in nature, the results could be subject to residual or unmeasured confounding. Furthermore, there were differences in classifications of fruit and vegetables across studies. The types consumed differed according to geographical locations. These factors could affect our results. Our subgroup analyses, however, showed that the associations between consumption and risk of all cause mortality did not differ significantly by study location.

Conclusions

This meta-analysis provides further evidence that higher consumption of fruit and vegetables is associated with a lower risk of mortality from all causes, particularly from cardiovascular diseases. The results support current recommendations to increase consumption to promote health and overall longevity.

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Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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What is already known on this topic

The association between fruit and vegetable consumption and risk of mortality has been examined in many studies, but the dose dependency of this association has not been determined in a meta-analysis

What this study adds

Higher consumption of fruit and vegetables is associated with a reduced risk of all cause mortality, with an average reduction in risk of 5% for each additional serving a day (6% for fruit and 5% for vegetables)

There was a threshold around five servings a day, after which the risk of death did not reduce further

There was a significant inverse association for cardiovascular mortality, but higher consumption was not appreciably associated with cancer mortality

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Tables

Table 1 Characteristics of studies included in meta-analysis of associations of fruit and vegetable consumption with risk of mortality

First author	Publication year	Country	Study name	No of participants	Age at baseline (years)	Years of follow-up (person years)	Mortality endpoints (No of cases)
Bellavia[44]	2013	Sweden	Swedish Mammography Cohort and Swedish Men Cohort	71 706*	45-83	13 (932 178†)	All cause (11 439)
Leenders[43]	2013	10 European countries	EPIC	451 151*	25-70	13 (5 864 963†)	All cause (25 682), CVD (5125), cancer (10 438)
Zhang[13] (men)	2011	China	Shanghai Men's Health Study	61 500	40-74	4.6 (282 900)	All cause (1951), CVD (635), cancer (853)
Zhang[13] (women)	2011	China	Shanghai Women's Health Study	74 942	40-70	10.2 (764 408)	All cause (3442), CVD (1023), cancer (1485)
Nagura[11]	2009	Japan	Japan Collaborative Cohort	59 485*	40-79	13 (756 054)	All cause (7606), CVD (2243)
Nakamura[12]	2008	Japan	Takayama Study	29 079*	≥35	7 (201 156)	CVD (384)
Tucker[45]	2005	US	Baltimore Longitudinal Study of Aging	501‡	34-80	18 (9018)	All cause (306)
Genkinger	2004	US	Odyssey Cohort	6 151*	30-93	12 (14 960)	All cause (910), CVD (378), cancer (307)
Steffen[46]	2003	US	Atherosclerosis Risk in Communities	11 940*	45-64	11 (131 340†)	All cause (867)
Sauvaget[47]	2003	Japan	Life Span Study	38 540*	34-103	18 (693 720†)	Cancer (3136)
Bazzano	2002	US	NHANES I	9 608*	25-74	19 (159 304)	All cause (2530), CVD (1145)
Rissanen[48]	2002	Finland	Kuopio Ischaemic Heart Disease Risk Factor	2641‡	42-60	12.8 (33 800)	All cause (485), CVD (245)
Strandhagen[9]	2000	Sweden	Study of Men Born in 1913	792‡	54-80	26 (20 592)	All cause (390), CVD (226), cancer (121)
Whiteman[49]	1999	UK	Oxford and Collaborators Health Check	11 090*	35-64	9 (93 464)	All cause (598), cancer (257)
Hertog[50]	1996	UK	Caerphilly Study	2112‡	45-69	13.8 (6874)	Cancer (114)
Sahyoun[51]	1996	US	Community dwelling volunteers	725*	60-101	12 (8700†)	All cause (217), CVD (108), cancer (64)
Colditz[20]	1985	US	Cohort study of Massachusetts residents aged ≥66	1271*	≥66	5 (6355†)	Cancer (42)

CVD=cardiovascular disease; EPIC=European Prospective Investigation into Cancer and Nutrition; NHANES I=first National Health and Nutrition Examination Survey.

*Men and women.

†Person time estimated by multiplying number of participants by average follow-up time.

‡Men.

Table 2 Characteristics of prospective studies of fruit and vegetable consumption in relation to mortality: exposure and outcome assessment, exposure levels, and covariates

Study	Exposure assessment method	Measure of associations	Outcome assessment	Categories of consumption	Covariates in fully adjusted model
Bellavia, 201344	FFQ. Self administered	HR	Ascertained through linkage to Swedish Register of Death Causes at National Board of Health and Welfare	Fruit and vegetables (servings/day): 0, 0.5, 1, 2, 3, 4, 5, 8	Age, sex, BMI, physical activity, smoking, alcohol, energy intake, educational level
Leenders, 2013[43]	Country specific FFQ and 7 day record	HR	Record linkage with cancer registries, boards of health, and death indices, or active follow-up	Fruit and vegetables (g/day): 178.8, 316.8, 468.4, 725.4. Fruit (g/day): 74.6, 159.9, 250.1, 403.0. Vegetables (g/day): 91.1, 151.6, 215.6, 339.4	Age, sex, centre, BMI, smoking status, smoking duration, time since stopped smoking, number of cigarettes smoked a day, alcohol consumption, physical activity, education, processed meat consumption, vegetables and fruit *()*
Zhang, 2011[13] (men)	FFQ. Interviewer administered	HR	Biennial home visits, record linkage to Shanghai Cancer Registry and Shanghai Vital Statistics Registry, and death certificates	Fruit (g/day): 14, 71, 129, 196, 308. Vegetables (g/day): 144, 232, 307, 398, 583	Age, BMI, education, occupation, family income, smoking, alcohol, physical activity, multivitamin supplement use, intakes of total energy and saturated fat, history of coronary heart disease, stroke, hypertension, or diabetes
Zhang, 2011[13] (women)	FFQ. Interviewer administered	HR	Biennial home visits, record linkage to Shanghai Cancer Registry and Shanghai Vital Statistics Registry, and death certificates	Fruit (g/day): 62, 155, 238, 330, 489. Vegetables (g/day): 124, 196, 261, 345, 506	As above
Nagura, 2009[11]	FFQ. Self administered, but confirmed by comparing two questionnaires administered 1 year apart	HR	Reviewing death certificates	Fruit (servings/day): 0.9, 2.3, 3.9, 5.9. Vegetables (servings/day): 1.2, 2.3, 3.4, 5.2	Age, BMI, sex, smoking status, alcohol intake, physical activity, hours of sleep, education years, perceived mental stress, cholesterol intake, SFA intake, n-3 fatty acids intake, sodium intake and histories of hypertension and diabetes, vegetable and bean intake (for fruit)/fruit and bean intake (for vegetable)
Nakamura, 2008[12]	FFQ. Interviewer administered. Validity and reproducibility of FFQ demonstrated by comparing it with other dietary assessment methods	HR	Data from office of National Vital Statistics	Men: fruit (servings/day): 0.3, 0.7, 1.3, 2.6; vegetables (servings/day): 2.2, 3.4, 4, 7.1. Women: fruit (servings/day): 0.4, 0.9, 1.5, 2.7; vegetables (servings/day): 2.5, 3.6, 4.8, 7.4	Age, BMI, total energy, marital status, years of education, smoking, alcohol, physical activity, history of hypertension or diabetes, menopausal status, dietary confounders (total protein, saturated fat, sodium intake)
Tucker, 2005[45]	7 day diet record. Self completed, but ambiguous or incomplete records clarified by telephone interview	HR	Cause of death determined by consensus of three physicians using death certificates, hospital and physician records, and autopsy data	Fruit and vegetables (servings/day): 0-5, ≥5	Age, total energy intake, saturate fat, BMI, smoking, alcohol, physical activity, dietary supplement use, saturated fat intake, and secular trend (year of first visit before *v* after 1980)
Genkinger, 2004[8]	FFQ. Self administered	HR	Death certificates	Fruit and vegetables (servings/day): 0.87, 1.61, 2.31, 3.21, 4.89	Age, BMI, smoking status, cholesterol concentration, energy intake
Steffen, 2003[46]	FFQ. Interviewer administered. One repeated measurement during follow-up	HR	Events investigated and validated by using hospital records, and deaths investigated and validated by using physician records and next-of-kin interview	Fruit and vegetables (servings/day): 1.5, 2.5, 3.5, 5.0, 7.5	Age, BMI, race, sex, and time dependent energy intake, education, smoking, physical activity, alcohol, hormone replacement in women, waist:hip ratio, systolic blood pressure, and use of antihypertensive drugs
Sauvaget, 2003[47]	FFQ. Self administered. Questionnaire compared with records of 24 hour dietary survey	HR	Nationwide family registration system	Fruit (servings/week): 0-1, 2-4, 5-7; vegetables (servings/week): 0-1, 2-4, 5-7	Age, BMI, sex, radiation dose, city, smoking status, alcohol habits, education level
Bazzano, 2002[7]	FFQ. Interviewer administered	HR	Death certificates and hospital discharge diagnosis	Fruit and vegetables (times/day): <1, 1, 2, ≥3	Age, sex, race, total energy intake, history of diabetes, physical activity, education, alcohol consumption, smoking, vitamin supplement use

(continued)

Study	Exposure assessment method	Measure of associations	Outcome assessment	Categories of consumption	Covariates in fully adjusted model
Rissanen, 2002[48]	4 day food record. Interviewer administered	HR	Linkage to national death registry using Finnish social security number	Fruit and vegetables (g/day): <133, 133-214, 215-293, 294-408, >408	Age, BMI, examination years, urinary excretion of nicotine metabolites and alcohol consumption, systolic and diastolic blood pressure, diabetes, serum LDL, HDL and triglycerides, maximal oxygen uptake, dietary factors (energy adjusted intakes of vitamin C and E, β carotene, lycopene, folate and fibre)
Strandhagen, 20009	FFQ. Interviewer administered	Total number of patients and numbers of events reported	Death certificates and autopsy records	Fruit (times/week): 0-1, 2-3, 4-5, 6-7; vegetables (times/week): 0-1, 2-3, 4-5, 6-7	Same age for all participants
Whiteman, 1999[49]	Self completed simple food frequency questions	HR	Confirmed by the Office for National Statistics	Fruit (times/week): 0-1, 1-3, 4-7; vegetables (times/week): 0-1, 1-3, 4-7	Age, sex, smoking
Hertog, 1996[50]	FFQ. Self administered, validated against weighed 7 day food record	HR	Death certificates	Fruit (g/day): 0-27, 28-70, 71-118, >118; vegetables (times/week): 0-79, 80-112, 113-149, >149	Age, BMI, smoking, social class, alcohol, energy intake, fat intake
Sahyoun, 1996[51]	3 day food record. Self completed	HR	Annual index of deaths and death certificates	Fruit (g/day): <163.8, 163.8-301, 301-437.6, >437.6; vegetables (g/day): <89.2, 89.2-187, 187-274.8, >274.8	Age, sex, disease status, disabilities affecting shopping
Colditz, 198520	FFQ. Interviewer administered	HR*	Confirmed by Massachusetts vital statistics register	Vegetables (servings/day): <0.7, 0.7-1.0, 1.1-1.5, 1.6-2.1, ≥2.2	Age

BMI=body mass index; FFQ=food frequency questionnaire; HDL=high density lipoprotein; HR=hazard ratio; LDL=low density lipoprotein; SFA=saturated fatty acid.

*Confidence intervals not reported.

Table 3| **Meta-analysis of fruit and vegetable consumption and risk of all cause, cardiovascular, and cancer mortality**

Comparison	No of studies	Cases/participants	Pooled HR* (95% CI), P value	Heterogeneity (I^2), P value	Begg's test, Egger's test
All cause mortality					
Fruit and vegetables combined	7[7 8 43-46 48]	42 219/553 698	0.95 (0.92 to 0.98), 0.001	82, <0.001	0.76, 0.006
Fruit	7[9 11 13 43 45 49 51]	40 192/660 186	0.94 (0.90 to 0.98), 0.002	77, <0.001	0.54, 0.02
Vegetables	7[9 11 13 43 45 49 51]	40 192/660 186	0.95 (0.92 to 0.99), 0.006	86, <0.001	0.13, 0.36
Cardiovascular mortality					
Fruit and vegetables combined	4[7 8 43 48]	6893/469 551	0.96 (0.92 to 0.99), 0.02	42, 0.16	0.73, 0.08
Fruit	6[9 11-13 43 51]	9744/677 674	0.95 (0.91 to 1.00), 0.03	71, 0.004	0.90, 0.28
Vegetables	6[9 11-13 43 51]	9744/677 674	0.96 (0.93 to 0.99), 0.01	63, 0.02	0.88, 0.73
Cancer mortality					
Fruit and vegetables combined	2[8 43]	10 745/457 302	0.97 (0.90 to 1.03), 0.31	68, 0.08	—
Fruit	7[9 13 43 47 49-51]	16 468/640 852	0.99 (0.97 to 1.00), 0.05	14, 0.33	0.37, 0.19
Vegetables	8[9 13 20 43 47 49-51]	16 510/642 123	0.99 (0.97 to 1.01), 0.19	37, 0.13	0.27, 0.13

HR=hazard ratio.

*Per serving/day.

Table 4| Stratified analysis on associations of fruit and vegetable consumption and all cause mortality

	Combined				Fruits				Vegetables			
	No	HR* (95% CI)	P value†	I^2 (%)	No	HR* (95% CI)	P value†	I^2 (%)	No	HR* (95% CI)	P value†	I^2 (%)
Location:												
US	4	0.95 (0.92 to 0.97)	0.25	27.4	2	0.94 (0.86 to 1.02)	0.80	0.0	2	0.85 (0.67 to 1.07)	0.03	79.6
Europe	3	0.96 (0.91 to 1.00)	0.01	88.6	3	0.93 (0.84 to 1.02)	0.02	73.2	3	0.91 (0.82 to 1.01)	0.01	83.3
Asia	—	—	—	—	2	0.93 (0.90 to 0.96)	0.28	13.5	2	0.98 (0.92 to 1.05)	0.01	95.6
Sex:												
Men and women	5	0.96 (0.93 to 0.99)	0.01	86.5	5	0.94 (0.90 to 0.99)	0.01	82.3	5	0.95 (0.92 to 0.99)	0.01	90.6
Men	2	0.94 (0.89 to 0.98)	0.53	0.0	2	0.91 (0.85 to 0.98)	0.65	0.0	2	0.95 (0.90 to 1.01)	0.75	0.0
Follow-up time (years):												
≥13	4	0.97 (0.94 to 1.00)	0.01	82.0	4	0.94 (0.88 to 1.00)	0.01	80.0	4	0.98 (0.95 to 1.02)	0.01	79.1
<13	3	0.93 (0.91 to 0.96)	0.36	1.3	3	0.94 (0.91 to 0.97)	0.39	0.0	3	0.82 (0.67 to 1.00)	0.01	88.0
Study quality score:												
≥8	5	0.96 (0.93 to 0.99)	0.01	82.4	2	0.95 (0.88 to 1.03)	0.01	90.5	2	0.98 (0.95 to 1.04)	0.01	92.7
<8	2	0.93 (0.89 to 0.96)	0.30	8.9	5	0.93 (0.91 to 0.96)	0.65	0.0	5	0.89 (0.83 to 0.96)	0.01	76.3
No of participants:												
≥10 000	3	0.96 (0.91 to 1.00)	0.01	89.2	4	0.94 (0.89 to 0.99)	0.01	86.6	4	0.96 (0.93 to 1.00)	0.01	91.3
<10 000	4	0.94 (0.91 to 0.97)	0.20	36.1	3	0.92 (0.87 to 0.98)	0.80	0.0	3	0.90 (0.80 to 1.01)	0.04	69.0

HR=hazard ratio.

*Per serving/day.

†P for heterogeneity.

Figures

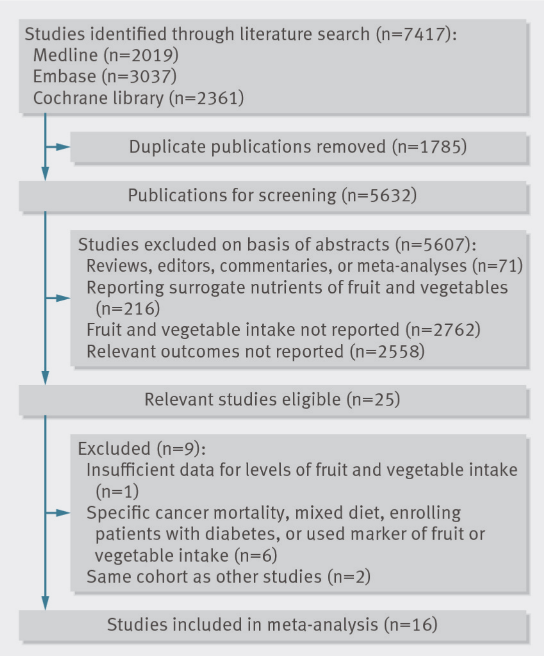

Fig 1 Selection of studies investigating effect of fruit and vegetable consumption on mortality

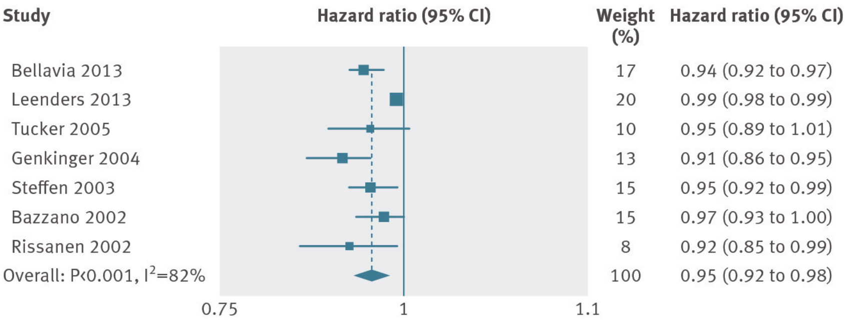

Fig 2 Risk of all cause mortality associated with servings/day of fruit and vegetables. Weights are from random effects analysis

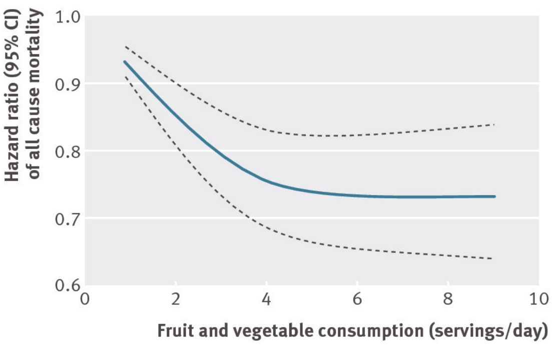

Fig 3 Dose-response relation between fruit and vegetable consumption and risk of all cause mortality

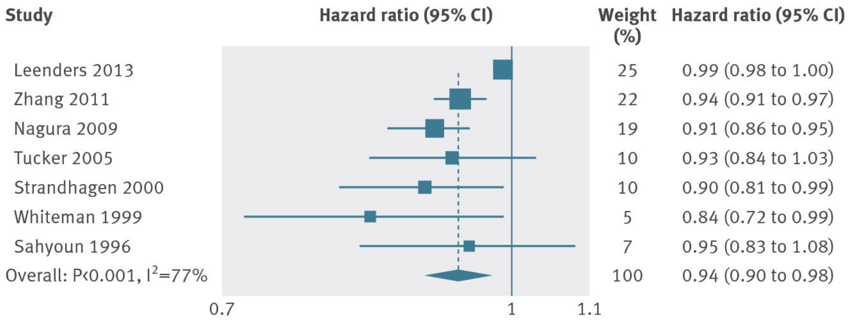

Fig 4 Risk of all cause mortality associated with servings/day of fruit. Weights are from random effects analysis

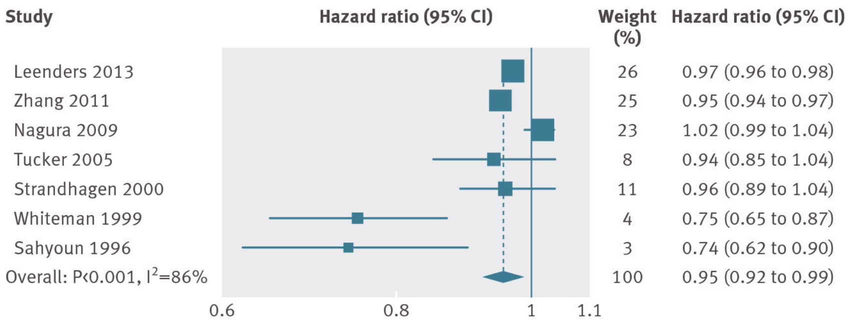

Fig 5 Risk of all cause mortality associated with servings/day of vegetables. Weights are from random effects analysis